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EVIDENCE FOR THE DEATH IN UTERO OF THE HOMOZYGOUS YELLOW MOUSE[1]

HEMAN L. IBSEN AND EMIL STEIGLEDER

Cuenot (1905) and Castle and Little (1910) have presented conclusive evidence that yellow mice are always heterozygous and hence cannot be made to breed true. Their combined results show that when yellows are mated together the proportion of yellows to non-yellows in the offspring is almost exactly 2:1 instead of the usual 3:1 ratio resulting from the mating of heterozygotes. Castle and Little seem justified on this account in assuming that the homozygous yellows are not viable, especially since the size of litter from the yellow × yellow mating is markedly smaller than that obtained from yellow × non-yellow or non-yellow × non-yellow matings.

Until quite recently no attempt had been made to determine embryologically the actual fate of the homozygous yellows. Since the present investigation was begun, however, Kirkham (1917) has published a preliminary statement of the results of such a study. His results, presented only in abstract, show that of 69 embryos from yellow × yellow parents, 26 or 37.8 per cent. were degenerating. For "non-yellows" he used albinos.[2] Of the 84 embryos from albino parents, only 2, or 2.3 per cent., were degenerating. This makes it seem quite probable that the homozygous yellow zygote develops for a time and then dies.

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[1] Papers from the Department of Experimental Breeding, Wisconsin Agricultural Experiment Station, No. 11. Published with the approval of the Director of the Station.

[The problem of the fate of the homozygous yellow mouse was undertaken at my suggestion during the summer of 1916 by Mr. Steigleder and the experimental work on which the present paper is based was done entirely by him. As he was, however, unable to complete the problem the accumulated material and records were turned over to Dr. Ibsen, who has checked all records with the preserved embryos and is alone responsible for the tabulation, interpretation and presentation of the results.—L. J. Cole.]

[2] This selection of albinos for "non-yellows" was unfortunate, since they apparently were not tested genetically, and hence may or may not have carried the factor for yellow. From the fact that the proportion of dead embryos was markedly different we may accept Kirkham's assump-

In our study no attempt has been made to investigate the very early stages, as was done by Kirkham, but a large number of embryos have been obtained from non-suckling females pregnant from 13 to 19 days.[3] In all 688 embryos have been examined. These have been obtained from (1) yellow females mated to yellow males, (2) yellow females mated to non-yellow males (chocolates), (3) non-yellow females (chocolates) mated to yellow males, and (4) non-yellow females mated to non-yellow males. In this last mating most of the parents were self blacks.

During the investigation two distinct types of dead embryos were encountered, (1) those in which development had ceased shortly after implantation, corresponding to those described by Kirkham, and (2) a few which seem to have developed normally till about the thirteenth day and then died, presumably because of overcrowding in the uterus. These latter were characterized by their dead, yellow appearance and smaller size as contrasted with the living pink color and larger size of the normal embryos. The first kind has been designated "dead embryos *A*" in the tables, while the second kind is classed as "dead embryos *B*." We are primarily concerned with "dead embryos *A*," and it is to be understood that reference is to this type unless specifically stated otherwise.[4] Similarly, by "living embryos" we mean those which

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tion that they were really genetically non-yellows, though this brings the argument dangerously close to reasoning in a circle. In our work a number of albinos were mated both to yellows and to non-yellows, but since the genetic constitution of the albinos was not sufficiently established in most cases, the embryos from these matings are not included in our tabulations.

[3] The normal duration of gestation in the mouse is about 21 days, but it is often less.

[4] We are indebted to Dr. Alva Wilson for sectioning for us dead embryos from each of the four types of matings. Microscopical examination of these has verified our previous conclusions as to their character.

were obviously alive when the mother was killed. As the females were killed by chloroforming, all embryos were usually dead by the time they were examined. The following tables give the results obtained. Each of the first four tables represents one of the four types of matings described above. In a few instances there has been some uncertainty as to the exact stage of gestation at which the embryos were removed, but in such cases this has been determined approximately by means of weights of the living embryos.

TABLE I

Yellow ♀ × Yellow ♂

Stage of Gestation	No. of Litters	Living Embryos	Dead Embryos *A*	Dead Embryos *B*	Percentage Dead Embryos *A*	Average Size of Litter	
						Living Embryos	Total Embryos
13 days......	5	33	14		29.8	6.6	9.4
14 days......	6	50	9		15.3	8.3	9.8
15 days......	4	26	10	1	27.0	6.5	9.3
16 days......	7	42	13	2	22.8	6.0	8.1
17 days......	5	25	4		13.8	5.0	5.8
18 days......	5	27	13		32.5	5.4	8.0
19 days......	1		4		100.0		4.0
Total......	33	203	67	3	24.54	6.15	8.27

TABLE II

Yellow ♀ × Non-yellow ♂

Stage of Gestation	No. of Litters	Living Embryos	Dead Embryos *A*	Dead Embryos *B*	Percentage Dead Embryos *A*	Average Size of Litter	
						Living Embryos	Total Embryos
13 days......	5	34	12		26.1	6.8	9.2
14 days......	6	56	1		1.8	9.3	9.5
15 days......	4	35	4		10.3	8.8	9.8
16 days......	2	14	8		36.4	7.0	11.0
17 days......	3	25	1		3.8	8.3	8.7
18 days......	3	17	1	1	5.3	5.7	6.3
19 days......	1	10				10.0	10.0
Total	24	191	27	1	12.33	7.96	9.13

The data presented agree in the main with Kirkham's, but our percentage of dead embryos *A*, from the yellow × yellow mating (Table I) is considerably less than his, while our percentage from the non-yellow × non-yellow mating (Table IV) is somewhat higher. Theoretically, if we assume that a certain proportion of embryos of other gametic composition die from unknown causes in mice of all colors and that all the homozygous yellows are represented as dead embryos, then the difference between the percentages of dead embryos from the yellow × yellow mating and the non-yellow × non-yellow mating should be approximately 25 per cent. In our results the difference is 19.2 per cent., while in Kirkham's it is 35.5 per cent. Neither of these is especially close to the expected percentage. If, however, his results and ours are combined the difference is 23.0 per cent., which is close to expectation.

TABLE III

NON-YELLOW ♀ × YELLOW ♂

Stage of Gestation	No. of Litters	Living Embryos	Dead Embryos *A*	Dead Embryos *B*	Percentage Dead Embryos *A*	Average Size of Litter	
						Living Embryos	Total Embryos
13 days......	1	2	1		33.3	2.0	3.0
14 days......	1	6				6.0	6.0
15 days......	2	15				7.5	7.5
16 days......	2	20	1	1	4.5	10.0	11.0
17 days......	2	11				5.5	5.5
18 days......	1	8	1		11.0	8.0	9.0
19 days......							
Total......	9	62	3	1	4.55	6.89	7.33

TABLE IV

NON-YELLOW ♀ × NON-YELLOW ♂

Stage of Gestation	No. of Litters	Living Embryos	Dead Embryos *A*	Dead Embryos *B*	Percentage Dead Embryos *A*	Average Size of Litter	
						Living Embryos	Total Embryos
13 days......	3	22	3		12.0	7.3	8.3
14 days......	3	28	1		3.4	9.3	9.7
15 days......							
16 days......	3	22		2		7.3	8.0
17 days......	3	19				6.3	6.3
18 days......	3	26	3		10.3	8.7	9.7
19 days......	1	4				4.0	4.0
Total......	16	121	7	2	5.38	7.56	8.13

If instead of comparing yellow × yellow with non-yellow × non-yellow only, all matings other than yellow

× yellow are combined for this purpose, it is found that the dead embryos in these combined matings constitute 8.9 per cent. of all embryos present. Subtracting this from 24.5, the per cent. of dead embryos in the yellow × yellow mating, the difference is only 15.6 per cent. When all these results are combined with those of Kirkham the difference is still only 19.4 per cent., which is considerably lower than that obtained by using only the classes considered by him. An attempt will be made farther on to explain this deficiency.

Tables II and III, representing the reciprocal crosses of yellow × non-yellow, show marked contrasts in several respects. In the yellow ♀ × non-yellow ♂ mating (Table II) 12.3 per cent. of the embryos were dead, while in the non-yellow ♀ × yellow ♂ mating (Table III) the percentage is only 4.5 per cent. For both matings the percentage of dead embryos theoretically should be the same as in the non-yellow × non-yellow mating (Table IV), since in neither case is there the possibility of any of the offspring being homozygous yellows. The percentage in Table III is approximately the same as in Table IV, but in Table II it is much higher. It is well known that yellow females tend to take on more fat than females of other colors. There is a possibility that this physiological difference may also in some way influence the production of a greater number of dead embryos *A*. This is offered merely as a suggestion, since there is no direct evidence for or against it.

In discussing the stages of pregnancy in which the dead embryos are to be found, Kirkham makes a statement which does not accord with our observations. He says: "No degenerating embryos have been found in either white [albino] or yellow mice pregnant more than sixteen days." He believes complete resorption of the degenerating embryos has taken place by the end of the sixteenth day. Table V, which is a summary of all our four types of matings, indicates that in our material there is no marked decrease in the percentage of dead embryos toward the end of pregnancy.

TABLE V

RELATION OF DEAD EMBRYOS TO STAGE OF PREGNANCY FOR THE FOUR TYPES OF MATINGS

Stage of Gestation	Dead Embryos *A*	Total Embryos (Including *B*)	Percentage of Dead Embryos *A*
13 days	30	121	24.8
14 days	11	151	7.3
15 days	14	91	15.4
16 days	22	125	17.6
17 days	5	85	5.9
18 days	18	97	18.6
19 days	4	18	22.2
Total	104	688	15.12

As previously stated, Cuénot, and Castle and Little noted that the average number per litter is less from yellow females mated to yellow males than from any other type of mating. Our results, summarized in Table VI, bear this out. Here it will be noted that the average number of living embryos is less for mating 1 than for any of the other types of matings singly or combined. It is evident that the average number of living embryos per litter represents those which would in the regular course of events have been born alive. In the yellow × yellow mating the average is only 6.15,[5] while for the other matings combined it is 7.63. The average number when the dead embryos are also included should be approximately the same in both cases, and this proves to be true, being 8.27 for yellow × yellow and 8.47 for all other matings.

TABLE VI

LITTER SIZE FOR THE DIFFERENT TYPES OF MATINGS

Type of Mating	No. of Litters	Average Number of Embryos per Litter		
		Living Embryos	Dead Embryos *A* and *B*	Total
1. Yellow ♀ × yellow ♂	33	6.15	2.12	8.27
2. Yellow ♀ × non-yellow ♂	24	7.96	1.17	9.13
3. Yellow ♂ × non-yellow ♀	9	6.89	0.44	7.33
(2 and 3 combined)	33	7.67	0.97	8.64
4. Non-yellow ♀ × non-yellow ♂	16	7.56	0.57	8.13
(2, 3 and 4 combined)	49	7.36	0.84	8.47

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[5] Two of the litters in this mating were made up entirely of dead embryos *A* and therefore had no living embryos. So far as living embryos are concerned their size would be 0, and they have been included as such with the other litters produced by this mating.

During 1916–17, the period at which the embryological study was carried on, numerous living litters of mice were born in the laboratory. Miss Sarah V. Jones, who was also working with mice, has generously furnished data from her own breeding experiments, and these have been incorporated with ours. Some of the mice in her experiments were black-and-tans, but as Dunn (1916) has shown that these are a form of yellow and are also always heterozygous, they have been classified as yellows. Table VII shows the average size of litters for the various types of matings.

TABLE VII

AVERAGE SIZE OF LITTERS BORN DURING 1916–17

(Figures in parentheses indicate the number of litters.)

Type of Mating	Average Number of Mice per Litter	
Type of Mating	At Birth	At Time Color was Recorded
1. Yellow ♀ × yellow ♂	5.36(140)	4.55(121)
2. Yellow ♀ × non-yellow ♂	6.21(88)	5.63(71)
3. Yellow ♂ × non-yellow ♀	7.02(50)	5.95(46)
(2 and 3 combined)	6.51(138)	5.76(117)
4. Non-yellow ♀ × non-yellow ♂	6.88(42)	5.49(37)
(2, 3 and 4 combined)	6.59(180)	5.69(154)

It will be seen that there is a deficiency of litter size from the yellow × yellow mating here as in the embryological material. Theoretically the average size of litter from yellow parents should be 75 per cent. of that from any of the other matings. Both Cuénot, and Castle and Little, however, have found it to be above 80 per cent. Our results are in accord with these findings.[6] Table VIII shows the percentages found by the various investigators. In order to make them comparable with the others our results as given in the table are for the living litters only and do not include the data from the embryological investigations.

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[6] Miss Durham (1911) found very little difference in average litter size between the offspring from yellows × yellows and the offspring from matings where at least one of the parents was a non-yellow. She says: "Only mice which lived long enough to have their colors determined are included in these averages." It seemed possible to us that she had not found any

TABLE VIII

PROPORTIONATE SIZE OF LITTERS FROM YELLOW × YELLOW AND YELLOW × NON-YELLOW MATINGS

(Figures in parentheses represent number of litters.)

Authority	Average Size of Litter		Ratio of "Yellow × Yellow" to "Yellow×Non-yellow"
	Yellow×Yellow	Yellow×Non-yellow	
Cuénot (1909)	3.38(50)	3.74(50)	90.37 %
Castle and Little (1910)	4.71(277)	5.57(325)	84.63 %
Ibsen and Steigleder, 1917	5.36(140)	6.51(138)	82.33 %

The most striking fact brought out in this table is that as the average size of the litters increases the ratio tends to decrease and therefore to approach 75 per cent. It would seem from this that if one could secure a race of mice having a high enough average per litter the theoretical percentage could be obtained. Using Table VIII as a basis for computation, such a race should average approximately 10 young per litter in the non-yellow × yellow mating and consequently about 7.5 per litter for the yellow × yellow mating. It is not probable that a race of this sort exists.

Various theories have been advanced to explain this unexpectedly large litter size in the yellow × yellow mating. Two suggested by Castle and Little will be considered here. Both take as their starting-point that "the perishing of a pure [homozygous] yellow zygote makes possible the development of a certain number of *other* fertilized eggs." The explanation follows: "Two ways may be suggested in which this might come about. First, more eggs may normally be liberated at an ovulation than there are young born subsequently. In that case, failure of some eggs to become attached to the uterus may make the chances greater that the remainder will become at-

difference because the size of litter had not been recorded at birth. Our records have been gone over and the litter size found at the time the colors were recorded. Some litters did not live long enough to be recorded in this manner and hence could not be included. By referring to Table VII one can see that our results do not at all agree with Miss Durham's. As a matter of fact, in our material the percentage relation is lower than when the litter size was computed at birth, being almost exactly 79 per cent. when "yellow × yellow" is compared with "non-yellow × yellow."

tached, or the perishing of some may make the chances greater that the rest will successfully complete their development. Or secondly, the production of a relatively small number of young at one birth may lead indirectly to more free ovulation subsequently, and so to the production of a large litter at a second birth.''

It will be seen in the first place that the above theories are based on false premises. It was not known at the time these theories were proposed that the homozygous yellow zygote does *not* perish in the sense of disintegrating and finally disappearing. It merely ceases to develop after a certain stage has been reached, and then remains more or less stationary till parturition. It might still be maintained that since these undeveloped zygotes take up very little room there would still be the possibility for the ''other'' zygotes to develop. In that case the average number of total embryos (including dead embryos *A* and *B*) should be greater in the yellow × yellow mating than in the non-yellow × yellow mating. Our data, presented in Table VI, indicate that this is not the fact. The other theory that ''the production of a relatively small number of young at one birth may lead indirectly to more free ovulation subsequently, and so to the production of a larger litter at a second birth'' still remains a possibility so far as our data are concerned.

There are several other possibilities which seem worthy of consideration. Instead of looking for causes that tend to *increase* the size of litters from yellows × yellows it may be profitable to determine if possible causes that may *decrease* the size of litters from the non-yellow × yellow mating. The first and most obvious possibility is that overcrowding in the uterus may have this effect by causing the death of some of the embryos. However, none of our results bear this out. In the first place there are proportionately just as many dead embryos *B* (whose death is probably caused by overcrowding) in the one type of mating as in the other, and in the second place this would mean that for our race of mice, having a high average litter size, there should be a proportionately large death rate due to overcrowding, and this would tend to increase the percentage relation between "yellow × yellow" and the "non-yellow × yellow" instead of decreasing it, which actually is the case.

We know that dead embryos *B* do not materially decrease the litter size in the non-yellow × yellow mating, but on the other hand we have clear evidence that dead embryos *A* have a decided effect in this respect. The only manner we could postulate in which this could affect the litter-size percentage relation for the two contrasted types of matings would be to assume that in the yellow × yellow mating dead embryos *A* are due almost entirely to the fact of their being homozygous yellows, while in the non-yellow × yellow mating separate agencies are at work producing an appreciable number of deaths. If a more careful examination of dead embryos *A* should reveal rather easily distinguishable differences this explanation could be tested.

There is still another explanation which so far as we know has never been suggested, and which has more evidence in its favor than any of the others proposed. When yellows are mated to yellows it is to be expected that some of the litters, especially if they are small, will consist entirely of homozygous yellows. Since these do not complete development, the entire litter will be composed of dead embryos *A* and consequently there will be no living embryos born at parturition. Such a litter will therefore be of 0 size. In our embryological investigation two litters consisting entirely of dead embryos *A* were found in the yellow × yellow mating and none in the other types of matings. Even with these two litters of 0 size in the yellow × yellow mating the average size of litter as compared to the litters of the non-yellow × yellow mating was not sufficiently low to bring the percentage relation down to 75 per cent. It is, however, 80.18 per cent., which is appreciably lower than the percentage obtained from litters of animals allowed to give birth to their young. (See Table VIII.) In the latter case it would naturally be impossible to detect the litters of 0 size.

In our embryological study there were 33 litters in the yellow × yellow mating. Of these, as previously stated, two consisted entirely of dead embryos *A*. This means that for 31 litters containing living embryos there were two that did not, or 6.45 per cent. If we assume a like percentage of litters of 0 size with our 140 normally born litters from "yellow × yellow" (Table VIII) the total number of litters would be increased to 149 and their average size would be 5.04 instead of 5.36. Taking 5.04 as a basis for comparison with 6.51, the average size of litters from the non-yellow × yellow mating, we find that the percentage relation is 77.42 per cent. This is reasonably close to 75 per cent., the expected percentage. In this connection it may be well to call attention to a fact, previously stated, that as the average litter size increases the percentage relation tends to approach 75 per cent. This is exactly what one should expect. For with increased size of litter there would be fewer litters of 0 size, and the averages as actually found would more nearly represent the true averages.

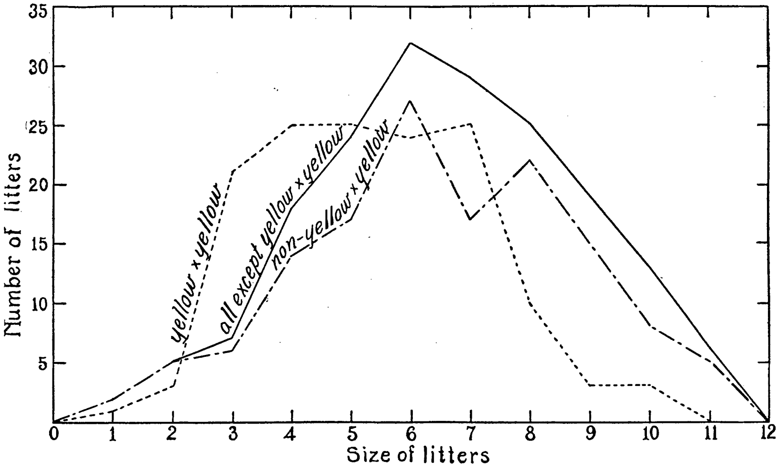

FIG. 1.

Curves (Fig. 1) have been constructed showing the frequency of the litter sizes for certain of the types of matings. The data upon which they are based may be found in Table IX. A careful survey of these curves, however, does not seem to lead to any very definite conclusions as to the special fitness of any of the various theories discussed in the preceding paragraphs. It will be seen that in the yellow × yellow mating there are proportionately more litters of small size and fewer of large size than are to be found in the other matings. This is what one should theoretically expect on all the theories.

TABLE IX

LITTERS BORN DURING 1916–17, CLASSIFIED ACCORDING TO NUMBER OF YOUNG IN LITTER

No. in Litter	Number of Litters			
	Yel. ♀ × Yel. ♂	Yel. ♀ × Non-yel. ♂	Yel. ♂ × Non-yel. ♀	Non.-yel. ♀ × Non.-yel. ♂
1	1	1	1	
2	3	3	2	
3	21	5	1	1
4	25	11	3	4
5	25	13	4	7
6	24	18	9	5
7	25	11	6	12
8	10	10	12	3
9	3	11	4	4
10	3	3	5	5
11		2	3	1
Total...	140	88	50	42

Summing up, we may say that all of our evidence tends to confirm the conclusion of Castle and Little that in mice homozygous yellow zygotes are produced in the yellow × yellow mating, but that these zygotes fail to develop normally after implantation in the uterus. Why this should be so is not evident and our investigation has not thrown any light on this point. It is possible a careful microscopical study of the embryos which die early might reveal some abnormality of development which would account for their failure to survive, but it is not probable that it would be of such a simple nature as the analogous cases of death of homozygous recessives lacking chlorophyll in corn and some other plants. It seems more probable that in mice there may be a "lethal factor," similar to those so well known in *Drosophila*, which is so closely linked to the factor for yellow that they are practically at the same locus and there is consequently no crossing over.

According to the investigations of Little (1915) an entirely similar condition obtains in regard to a dominant white spotting factor (*W*) in mice, which, like yellow, appears never to occur in a homozygous condition. Whether the homozygous individuals in this case also die at an early stage and might be found as dead embryos has not yet been determined. Little has, however, demonstrated (1917) that the two factors are independent in heredity, and that litters from yellows carrying *W*, mated *inter se*, average only three per litter (10 litters), while similar yellows mated to *ww* non-yellows have litters averaging 5 per litter (9 litters). Although the numbers are small the percentage relation for the two matings, 60 per cent., is quite close to the theoretical expectation, 56.3 per cent.

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